# Benefits of Antihypertensive Pharmacologic Therapy and Blood Pressure Reduction in Outcome Trials

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*In a quantitative overview of published trials, we investigated whether pharmacologic properties of antihypertensive drugs, as opposed to reduction in blood pressure, explain cardiovascular outcomes in hypertensive or high-risk patients. We used meta-regression to investigate the association between the odds ratios of outcome (experimental vs. reference treatment) and the corresponding blood pressure differences between study groups. Thus, we correlated odds ratios with between-group differences in systolic pressure. We then compared odds ratios of benefit observed in recent trials with those predicted by meta-regression on the basis of the differences in systolic pressure between randomized groups. Among nine actively-controlled trials in hypertension, significant differences in systolic pressure (follow-up minus baseline) between randomized groups (experimental minus reference) were observed in the ALLHAT, CAPPP, MIDAS, and NORDIL trials. Furthermore, the differences in achieved systolic and/or diastolic pressure between study groups were also significant in the hypertension trials and studies in high-risk patients, which involved untreated control patients. The differences between the observed odds ratios and those predicted by meta-regression did not reach statistical significance except for NORDIL and the single-drug therapy subgroup of the PROGRESS trial. In NORDIL, the risk of stroke was lower on diltiazem than on the older drug classes despite a 3.1 mm Hg higher systolic pressure on the calcium channel blocker. In PROGRESS, perindopril alone reduced blood pressure by 5/3 mm Hg, but did not affect the incidence of all cardiovascular events or the recurrence of stroke. In conclusion, the finding that in the reviewed trials blood pressure reduction largely accounted for outcome emphasizes the desirability of tight blood pressure control. The hypothesis that blood pressure-lowering medications might influence cardiovascular prognosis over and beyond their antihypertensive effect remains to a large extent unproved. (J Clin Hypertens. 2003;5:66–75)*


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Placebo-controlled trials in hypertension have shown that antihypertensive drugs reduce cardiovascular morbidity and mortality.[1,2] Recent outcome trials investigated the benefits associated with different levels of blood pressure control,[3,4] or compared older classes of antihypertensive drugs such as diuretics or β blockers with newer agents such as calcium channel blockers,[5–9] angiotensin-converting enzyme (ACE) inhibitors,[8,10,11] or the α blocker doxazosin.[12] Furthermore, placebo-controlled studies explored whether calcium channel blockers[13] or ACE inhibitors[14–16] may confer additional benefit over and beyond blood pressure lowering in specific groups of patients with cardiovascular renal disorders. In the Heart Outcomes Prevention Evaluation (HOPE)[14] and Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) studies,[12] significant differences between the randomized groups in systolic and/or diastolic pressure were observed. This makes the interpretation of the results difficult. For this reason, we

used meta-regression analysis to explore to what extent the morbidity and mortality results of recent outcome trials could be explained in terms of blood pressure reduction per se.[17]

More recently, four placebo-controlled outcome trials provided additional outcome results on treatment with antihypertensive drugs.[17–20] Three studies tested the efficacy of angiotensin II receptor antagonists in patients with diabetic nephropathy.[18–20] The Perindopril Protection Against Recurrent Stroke Study (PROGRESS)[21] investigated whether an ACE inhibitor alone or in combination with a diuretic would reduce stroke recurrence in patients with a history of minor stroke or transient ischemic attack. In this review, we update our meta-regression analysis, which was previously published elsewhere.[17]

## METHODS

### Data Acquisition

The inclusion and exclusion criteria for trials in the present analysis have been previously described.[17] Briefly, we searched for outcome trials that tested drugs with blood pressure-lowering action in normotensive or hypertensive patients who did not have overt congestive heart failure at baseline. Other inclusion criteria were a randomized controlled parallel group design, publication in a peer reviewed journal, evaluation of blood pressure and cardiovascular events, follow-up of 2 years or longer, and a sample size of 100 or more. In the present analysis, we included 24 trials in hypertension[3–12,22–36] and six placebo-controlled trials involving both normotensive and hypertensive subjects (Table I).[14–16,19,21,37] Among these 30 trials, two had a single-blind design with alternate allocation of consecutive patients to placebo or active treatment.[31,33]

In keeping with our inclusion criteria, we excluded 13 trials,[13,18,20,38–47] which included fewer than 100 subjects,[42–44] covered less than 2 years of follow-up,[39,41] or did not report systolic pressure[13,40,45,46] or the number of cardiovascular events.[18,20,38,47] We did not include a population-based trial[48] and actively-controlled trials that compared old with old drugs,[49–51] or new with new drugs,[52,53] because only a few such studies were available, and because it was difficult to define the reference group for the calculation of the odds ratios.

Because of the small number of events and similarity of trial design, in our analysis we combined three actively-controlled trials that tested a calcium channel blocker against a thiazide diuretic (the Multicenter Isradipine Diuretic Atherosclerosis Study [MIDAS],[36] National Intervention Cooperative Study in Elderly Hypertensives [NICS],[5] and Verapamil in Hypertension and Atherosclerosis Study [ VHAS][9]). For similar reasons, we also combined the Prevention of Atherosclerosis with Ramipril Trial (PART 2)[15] and Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT)[16] that compared ACE inhibitors with placebo in patients at high cardiovascular risk.

We based our analysis on summary statistics reported in the literature.[3–12,14–16,19,21,23–37,41,54–56] With the exception of fatal combined with nonfatal events in the European Working Party on High Blood Pressure in the Elderly (EWPHE) trial,[26,54] all outcome results were reported on the basis of an intent-to-treat principle. Within each trial, the reference group consisted of patients left untreated[34,35] or allocated placebo,[14,15,19,21,23–34,37,41] or the patients randomized to older drug classes[5–12,36] or to a treatment strategy leading to less blood pressure control.[3,4] We had to accept the definitions of events used by study investigators. However, whenever possible, all cardiovascular events included stroke, myocardial infarction, congestive heart failure, and cardiovascular or sudden death.

### Statistical Analysis

We used the SAS statistical package (SAS Institute, Cary, NC), version 8.1, to correlate odds ratios of experimental vs. reference treatment with the corresponding blood pressure differences. For these calculations, odds ratios were logarithmically transformed. The regression lines were weighted by the inverse of the variance of the individual odds ratios.[57] Net treatment effects on blood pressure were determined by subtracting the mean change in the experimental group (follow-up minus baseline) from the corresponding mean change in the reference group.

## RESULTS

The 30 studies included in the meta-regression represent 149,407 patients (Table I). They comprised nine actively controlled trials[5–12,36]: the Hypertension Optimal Treatment (HOT)[3] study that investigated different levels of blood pressure control, three placebo-controlled trials in isolated systolic hypertension (the Systolic Hypertension in the Elderly Program [SHEP],[28] Systolic Hypertension in China [Syst-China] trial,[33,58] and Systolic Hypertension in Europe [Syst-Eur] trial[32,59]), four placebo-controlled trials in normotensive or hypertensive patients at high cardiovascular or renal risk (HOPE,[14] PART 2,[15] SCAT,[16] and Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study [RENAAL][19]), two trials in patients with a history of minor stroke or transient

**Table I.** Characteristics of Trials

| Trial and Year of Main Publication* | Masking Type | No. of Patients | Experimental Treatment | Age (Mean [SD], Years) | Women (%) | CV Complications (%) | DM (%) | Mean SBP/DBP at Entry (mm Hg)† | Follow-Up (Years)‡ |
|---|---|---|---|---|---|---|---|---|---|
| Trials in Hypertension | | | | | | | | | |
| Active treatment vs. placebo | | | | | | | | | |
| VACS,[22] 1970 | Double | 380 | HCTZ + reserpine | 51 (NR) | 0 | NR | NR | 164/104 | 3.3 |
| HSCS,[23] 1974 | Double | 452 | Deserpine + methyclothiazide | 59 (NR) | 59 | 100 | 56 | 164/100 | 3.0 |
| USPHS,[24] 1977 | Double | 389 | HCTZ + rauwolfia | 44 (7) | 20 | 0 | 0 | 147/99 | 7.0 |
| ATMH,[25] 1980 | Single | 3427 | Chlorothiazide | 50 (9) | 37 | 7 | 0 | 157/100 | 4.0 |
| EWPHE,[26] 1985 | Double | 840 | HCTZ + triamterene | 72 (8) | 70 | 0 | 0 | 183/101 | 4.7 |
| MRC-1,[27] 1985 | Single | 17,354 | Bendrofluazide, propranolol | 52 (8) | 48 | 2 | 0 | 161/98 | 4.9 |
| SHEP,[28] 1991 | Double | 4736 | Chlorthalidone | 72 (7) | 57 | 43 | 10.1 | 170/77 | 4.5 |
| STOP-1,[29] 1991 | Double | 1627 | β Blockers, HCTZ/A | 76 (4) | 63 | NR | NR | 195/102 | 2.0 |
| MRC-2,[30] 1992 | Single | 4396 | HCTZ/A, atenolol | 70 (NR) | 58 | 18 | 0 | 185/91 | 5.8 |
| STONE,[31] 1996 | Single | 1632 | Nifedipine | 67 (5) | 53 | 0 | 0 | 169/98 | 2.5 |
| Syst-Eur,[32] 1997 | Double | 4695 | Nitrendipine | 70 (7) | 67 | 30 | 10.5 | 174/85 | 2.0 |
| Syst-China,[33] 1998 | Single | 2394 | Nitrendipine | 67 (6) | 36 | 11 | 3.8 | 170/86 | 3.0 |
| Active treatment vs. no treatment | | | | | | | | | |
| Oslo,[34] 1980 | Open | 785 | HCTZ | 45 (3) | 0 | 0 | 0 | 156/97 | 5.5 |
| HEP,[35] 1986 | Open | 884 | Atenolol | 69 (5) | 70 | 31 | 0 | 196/99 | 4.4 |
| Vigorous vs. moderate blood pressure lowering | | | | | | | | | |
| HOT,[3] 1998 | Open | 18,790 | Felodipine | 62 (8) | 47 | ≈9 | 8 | 170/105 | 3.8 |
| UKPDS,[4] 1998 | Open | 1148 | Captopril, atenolol | 56 (8) | 46 | NR | 100 | 160/94 | 8.4 |

**Table I.** Characteristics of Trials *(continued)*

| Trial and Year of Main Publication* | Masking Type | No. of Patients | Experimental Treatment | Age (Mean [SD], Years) | Women (%) | CV Complications (%) | DM (%) | Mean SBP/DBP at Entry (mm Hg)† | Follow-Up (Years)‡ |
|---|---|---|---|---|---|---|---|---|---|
| New vs. old antihypertensive drugs | | | | | | | | | |
| MIDAS,[36] 1996 | Double | 883 | Isradipine | 59 (9) | 22 | ≈4 | NR | 150/97 | 3.0 |
| VHAS,[9] 1997 | Open | 1414 | Verapamil (SR) | 53 (7) | 51 | 5 | 4 | 169/102 | 2.0 |
| UKPDS,[11] 2000 | Open | 758 | Captopril | 56 (8) | 45 | NR | 100 | 160/94 | 8.4 |
| NICS,[5] 1999 | Double | 414 | Nicardipine (SR) | 70 (7) | 67 | ≈28 | NR | 172/94 | 4.3 |
| STOP-2,[8] 1999 | Open | 6614 | ACEIs, DHPs | 76 (?) | 67 | ≈20 | 11 | 194/98 | 5.0 |
| CAPPP,[10] 1999 | Open | 10,985 | Captopril | 53 (8) | 47 | 4 | 5 | 161/99 | 6.1 |
| NORDIL,[7] 2000 | Open | 10,881 | Diltiazem | 60 (7) | 51 | ≈8 | 7 | 173/106 | 4.5 |
| INSIGHT,[6] 2000 | Double | 6321 | Nifedipine (GITS) | 65 (7) | 54 | ≈20 | 21 | 167/96 | 3.5 |
| ALLHAT,[12] 2000 | Double | 24,335 | Doxazosin | 67 (8) | 47 | 45 | 36 | 145/83 | 3.3 |
| Placebo-Controlled Trials Involving Hypertensive and Normotensive Subjects | | | | | | | | | |
| PATS,[37] 1995 | Double | 5665 | Indapamide | 60 (8) | 28 | 100 | NR | 154/93 | 2.0 |
| PART 2,[15] 2000 | Double | 617 | Ramipril | 61 (8) | 18 | 100 | 9 | 133/79 | 4.7 |
| SCAT,[16] 2000 | Double | 460 | Enalapril | 61 (9) | 11 | 100 | 11 | 130/78 | 4.0 |
| HOPE,[14] 2000 | Double | 9297 | Ramipril | 66 (7) | 27 | 88 | 39 | 139/79 | 4.5 |
| RENAAL,[19] 2001 | Double | 1513 | Losartan | 60 (7) | 37 | 100 | 100 | 153/82 | 3.4 |
| PROGRESS,[21] 2001 | Double | 6105 | Perindopril, indapamide | 64 (10) | 30 | 100 | 13 | 147/86 | 3.9 |

CV=cardiovascular; DM=diabetes mellitus; SBP/DBP=systolic/diastolic blood pressure; HCTZ=hydrochlorothiazide; HCTZ/A=hydrochlorothiazide/amiloride; SR=sustained release; ACEIs=angiotensin-converting enzyme inhibitors, DHPs=dihydropyridine calcium channel blockers (felodipine or isradipine); GITS=gastrointestinal therapeutic system; NR=not reported

UKPDS=United Kingdom Prosepective Diabetes Study; CAPPP=Captopril prevention project; INSIGHT=International Nifedipine GITS Study—Intervention as a Goal for Hypertensive Treatment

*Other trial acronyms are explained in the text of the article; †a large proportion of patients were on antihypertensive drugs in ALLHAT, PART 2, SCAT, HOPE, RENAAL and PROGRESS; ‡mean or median follow-up

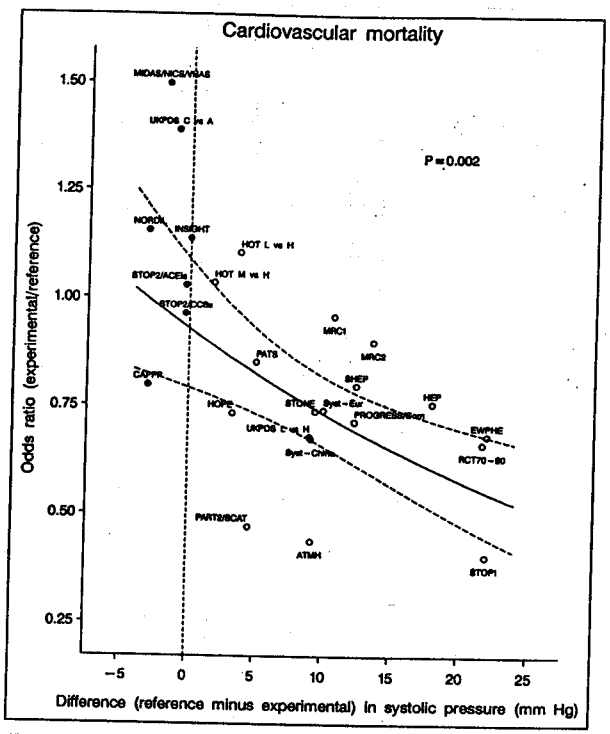


*Figure 1. Relationship between odds ratios (ORs) of experimental vs. reference treatment for cardiovascular mortality and corresponding between-group differences in systolic blood pressure (SBP). The regression line was plotted with 95% confidence interval, and was weighted for the inverse of the variance of individual OR. The negative association between OR and differences in SBP indicates that the more blood pressure was reduced by experimental treatment, the greater was the observed benefit. Acronyms are explained in the text of the article: HOT M vs. H (HOT trial—85 vs. 90 mm Hg as target diastolic pressure [DBP]); HOT L vs. H (HOT trial—80 vs. 90 mm Hg as target DBP); INSIGHT (International Nifedipine GITS Study—Intervention as a Goal for Hypertensive Treatment[6]); MIDAS/NICS/VHAS (combined results of the MIDAS, NICS and VHAS trials); PART 2/SCAT (combined results of the PART 2 and SCAT trials); PROGRESS/Per (PROGRESS stratum given only perindopril); PROGRESS/Com (PROGRESS stratum given combination therapy of perindopril and indapamide); RCT70-80 (combined results of four smaller trials published from 1970–1980: HSCS, OSLO Study, USPH Study, and VACS in patients with DBP averaging 90–114 mm Hg); STOP-2/ACEIs (ACE inhibitor arm of STOP-2 vs. old drugs); STOP-2/CCBs (calcium channel blocker arm of STOP-2 vs. old drugs); UKPDS C vs. A (UKPDS Hypertension in Diabetes Study—captopril vs. atenolol); UKPDS L vs. H (UKPDS Hypertension in Diabetes Study—low vs. high on-treatment blood pressure).*

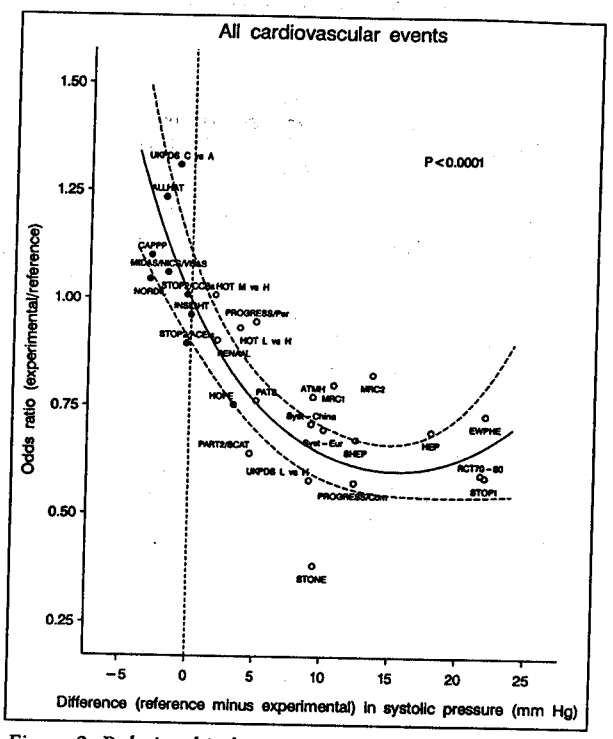


*Figure 2. Relationship between odds ratios of experimental vs. reference treatment for all cardiovascular events and corresponding between-group differences in systolic pressure. For further explanations, see legend to Figure 1.*

ischemic attack (Post-stroke Antihypertensive Treatment Study [PATS][37] and PROGRESS[21]), and 11 older trials testing the efficacy of antihypertensive drugs against no treatment (trial of hypertension in elderly patients in primary care [HEP][35] and Oslo Study on the Treatment of Mild Hypertension [OSLO][34]) or placebo (Australian Trial in Mild Hypertension [ATMH],[25] EWPHE,[26] Hypertension-Stroke Cooperative Study [HSCS],[23] Medical Research Council trial of treatment of mild hypertension [MRC-1],[27] Medical Research Council trial of treatment of hypertension in older adults [MRC-2],[30] Swedish Trial in Old Patients with hypertension [STOP-1],[29] Shanghai Trial of Nifedipine in the Elderly [STONE],[31] United States Public Health Service Hospitals Cooperative Study [USPHS][24] and Veterans Administration Cooperative Study in patients with diastolic pressure averaging 90–114 mm Hg [VACS][41]).

The meta-regression line between the odds of an event and the differences in systolic pressure between the study groups was linear for cardiovascular mortality (Figure 1), i.e., the greater the difference the greater the benefit. It was curvilinear for all fatal and nonfatal cardiovascular events (Figure 2). The meta-regression line was also curvilinear for stroke and myocardial infarction including sudden death, if these two specific cerebrovascular and cardiac end points were analyzed separately. We did not specifically investigate the relationship between the odds of congestive heart failure and the between-group differences in systolic pressure because few studies reported the incidence of heart failure as a separate outcome in the analysis.

Significant differences between the randomized groups (experimental minus reference) in systolic and/or diastolic pressure were observed in four

Table II. Observed Odds Ratios and Odds Ratios Predicted by the Difference in Systolic Pressure in Meta-Regression in Three Actively-Controlled Trials

| | Observed OR* | Predicted Mean OR† | Difference (%)‡ | P Value§ |
|---|---|---|---|---|
| ALLHAT[12] | | | | |
| CV events | 1.24 (1.15–1.33) | 1.14 (1.00–1.31) | –7.7 (–24.9 to 7.0) | 0.32 |
| Stroke | 1.18 (0.99–1.39) | 1.06 (0.93–1.21) | –10.8 (–36.8 to 10.2) | 0.34 |
| MI | 1.01 (0.88–1.16) | 1.13 (0.97–1.30) | 9.9 (–9.3 to 25.7) | 0.29 |
| CAPPP[10] | | | | |
| CV mortality | 0.80 (0.58–1.09) | 0.99 (0.82–1.21) | 20.0 (–15.1 to 44.4) | 0.22 |
| CV events | 1.10 (0.95–1.27) | 1.23 (1.06–1.45) | 11.1 (–9.5 to 27.7) | 0.27 |
| Stroke | 1.29 (1.03–1.61) | 1.14 (0.98–1.33) | –12.9 (–47.6 to 13.7) | 0.38 |
| MI | 1.01 (0.80–1.26) | 1.21 (1.01–1.43) | 16.2 (–11.0 to 36.7) | 0.22 |
| NORDIL[7] | | | | |
| CV mortality | 1.16 (0.89–1.50) | 1.00 (0.82–1.21) | –15.7 (–59.2 to 15.9) | 0.37 |
| CV events | 1.04 (0.91–1.20) | 1.24 (1.06–1.46) | 16.2 (–2.8 to 31.8) | 0.09 |
| Stroke | 0.81 (0.65–1.01) | 1.14 (0.98–1.34) | 29.0 (7.7 to 45.5) | 0.01 |
| MI | 1.19 (0.95–1.48) | 1.22 (1.01–1.45) | 2.1 (–29.4 to 26.0) | 0.88 |

OR=odds ratio; CV=cardiovascular; MI=myocardial infarction
*OR reported in the published articles. Values smaller than unity indicate benefit of experimental treatment compared with reference group; †mean OR (95% confidence interval) predicted by the meta-regression lines (see Figures 1 and 2); ‡difference between predicted minus observed OR (95% confidence interval) expressed in percent of the predicted OR. Positive and negative values indicate benefit and risk associated with experimental treatment beyond blood pressure reduction, respectively; §significance of the difference between observed and predicted ORs

actively-controlled trials (Figure 2). As expected, the differences in achieved systolic and/or diastolic pressure between study groups were also significant in the hypertension trials which involved untreated control patients,[23–35,41] as well as in other placebo-controlled trials.[14–16,19,21,37]

Further analyses compared the observed odds ratios with those predicted by the meta-regression lines for three actively-controlled trials[7,10,12] (Table II) and five placebo-controlled studies (Table III).[14–16,19,21] The authors of these reports suggested benefit or harm of the drugs tested over and beyond the effects on blood pressure. In contrast to their interpretation, the differences between the observed odds ratios and those predicted by the meta-regression lines (Figures 1 and 2) did not reach statistical significance except for the Nordic Diltiazem (NORDIL)[7] and PROGRESS trials.[21] In NORDIL, the risk of stroke was lower on diltiazem than on the older drug classes despite a 3.1 mm Hg higher systolic pressure. In the perindopril-only subgroup of the PROGRESS trial,[21] systolic pressure was reduced by 5 mm Hg, but monotherapy with the ACE inhibitor did not affect the risk of all cardiovascular events or stroke recurrence.

## DISCUSSION

In this updated meta-regression analysis, three trials (PATS,[37] RENAAL,[19] and PROGRESS[21]) were added and the number of patients increased from 136,124 to 149,407. The present results corroborated our previous findings.[17] Indeed, in trials in hypertensive patients and in studies including normotensive or hypertensive subjects at high cardiovascular risk, blood pressure gradients accounted for most of the differences in cardiovascular outcome. For fatal and nonfatal cardiovascular complications combined, most of the benefit of antihypertensive treatment was achieved by moderate differences in systolic pressure of approximately 15 mm Hg. In older patients with isolated systolic hypertension,[1] lowering blood pressure by 10 mm Hg systolic and 4 mm Hg diastolic decreased the risk of stroke, and myocardial infarction by 26% and 23%.[1] In patients with predominantly diastolic hypertension, the corresponding benefits produced by a 5–6 mm Hg decline in diastolic pressure were 38% and 16%, respectively.[2]

The HOPE trial[14,56] was a placebo-controlled study and included approximately 90% of patients with previous cardiovascular complications. At base-

**Table III.** Observed Odds Ratios and Odds Ratios Predicted by the Difference in Systolic Blood Pressure in Meta-Regression in Four Placebo-Controlled Trials

| | Observed OR* | Predicted Mean OR† | Difference (%)‡ | *P* Value§ |
|---|---|---|---|---|
| HOPE[14] | | | | |
| CV mortality | 0.73 (0.62–0.86) | 0.86 (0.75–0.98) | 14.6 (–4.7 to 30.4) | 0.13 |
| CV events | 0.76 (0.67–0.85) | 0.82 (0.75–0.90) | 8.2 (–5.5 to 20.2) | 0.23 |
| Stroke | 0.68 (0.62–0.86) | 0.77 (0.70–0.83) | 11.3 (–11.4 to 29.4) | 0.30 |
| MI | 0.79 (0.69–0.90) | 0.85 (0.77–0.92) | 6.5 (–9.2 to 19.9) | 0.40 |
| PART 2/SCAT[15,16] | | | | |
| CV mortality | 0.47 (0.21–0.98) | 0.83 (0.74–0.94) | 43.5 (–19.2 to 73.2) | 0.13 |
| CV events | 0.64 (0.44–0.94) | 0.78 (0.71–0.84) | 17.0 (–22.8 to 43.9) | 0.35 |
| MI | 0.63 (0.38–1.05) | 0.80 (0.73–0.87) | 20.7 (–32.0 to 52.3) | 0.37 |
| PROGRESS[21] | | | | |
| Combination therapy | | | | |
| CV mortality | 0.72 (0.55–0.95) | 0.69 (0.62–0.78) | –3.0 (–40.8 to 24.7) | 0.85 |
| CV events | 0.60 (0.51–0.71) | 0.61 (0.56–0.68) | 6.4 (–14.8 to 23.7) | 0.52 |
| Stroke | 0.57 (0.46–0.70) | 0.57 (0.51–0.62) | 2.5 (–23.3 to 23.0) | 0.83 |
| MI | 0.65 (0.48–0.88) | 0.69 (0.62–0.77) | 6.2 (–31.9 to 33.3) | 0.71 |
| Single-drug therapy | | | | |
| CV events | 0.96 (0.80–1.15) | 0.76 (0.70–0.83) | –24.4 (–55.3 to 0.4) | 0.05 |
| Stroke | 0.95 (0.77–1.19) | 0.71 (0.65–0.78) | –33.6 (–71.3 to –4.1) | 0.02 |
| RENAAL[19] | | | | |
| CV events | 0.90 (0.73–1.12) | 0.88 (0.81–0.96) | –2.3 (–29.3 to 19.0) | 0.85 |
| MI | 0.73 (0.49–1.08) | 0.89 (0.82–0.97) | 18.0 (–22.4 to 45.5) | 0.33 |

OR=odds ratio; CV=cardiovascular; MI=myocardial infarction
*OR reported in the published articles. Values smaller than unity indicate benefit of experimental treatment compared with reference group; †mean OR (95% confidence interval) predicted by the meta-regression lines (see Figures 1 and 2); ‡difference between predicted minus observed OR (95% confidence interval) expressed in percent of the predicted OR. Positive and negative values indicate benefit and risk associated with experimental treatment beyond blood pressure reduction, respectively; §significance of the difference between observed and predicted odds ratios

line and probably also during follow-up, a large proportion of patients in both the ramipril and placebo groups were treated with calcium channel blockers, diuretics, or β blockers. Compared with the placebo group, treatment with ramipril reduced cardiovascular mortality (–27%) and the incidence of stroke (–32%), myocardial infarction (–21%) and congestive heart failure (–23%).[14] There was a 3/1 mm Hg difference in blood pressure between the ramipril and placebo groups.[14] The hypothesis has been put forward that the endothelial actions of ramipril[56] might stabilize atherosclerotic plaques in large arteries.[60] ACE inhibitors have shown proven benefits in patients with heart failure[61] or dysfunction of the left ventricle.[62] However, our results suggest that blood pressure may account for most, if not all, of the benefit observed in the ramipril group. In addition, the results of other large trials of ACE inhibitors in hypertensive patients,[8,10] did not suggest a benefit of ACE inhibitors, which would not be explained by blood pressure.

Active antihypertensive treatment in the placebo-controlled PROGRESS study[21] was also based on an ACE inhibitor (perindopril). This double-blind trial demonstrated that among patients with a history of stroke or transient ischemic attack, blood pressure-lowering treatment with perindopril alone or in combination with indapamide reduced the risk of recurrent stroke by 28% and that of stroke, heart attack, or death from cardiovascular disease by

26%. However, a prespecified subgroup analysis revealed striking heterogeneity of treatment effect sizes for the risks of all cardiovascular events and stroke between participants who received perindopril plus indapamide and those who received perindopril alone. Combination therapy reduced blood pressure by 12/5 mm Hg, and decreased stroke and all cardiovascular events by 43% and 40%, respectively. Treatment with perindopril alone lowered blood pressure by 5/3 mm Hg, but did not affect stroke recurrence or the incidence of all cardiovascular events. The relative risk reductions observed in PROGRESS for the perindopril-only group deviated significantly from those predicted by the meta-regression, but those for combination therapy did not.

In the ALLHAT trial,[12] the patients randomized to doxazosin experienced higher rates of stroke and congestive heart failure than the patients given chlorthalidone. The ALLHAT investigators suggested that the observed blood pressure differences were sufficient to explain the higher incidence of stroke on doxazosin, but only a 10%–20% increase in the occurrence of heart failure, not a doubling of the rate.[12] However, for cardiovascular mortality, stroke, and myocardial infarction as well as all cardiovascular events including congestive heart failure, we did not find significant differences between the observed odds ratios and those expected on the basis of the blood pressure difference between the two treatment groups.

Three trials on angiotensin II receptor antagonists consistently demonstrated that this class of agents reduced the incidence of renal dysfunction in patients with diabetic nephropathy.[18–20] However, active treatment also reduced blood pressure, especially systolic pressure by 2–4 mm Hg. The RENAAL trial[19] reported the incidence of all cardiovascular events and myocardial infarction and hence was included in our meta-regression. The observed insignificant reduction in cardiovascular outcome in the RENAAL trial was not different from that predicted by the modest blood pressure difference between losartan and placebo.

Our overview should be interpreted within the context of its limitations. As in all meta-analyses that start from published summary statistics, we achieved less standardization than is attainable in quantitative overviews based on individual patient data. We did not correct for regression dilution bias.[1,63] However, clinicians cannot leave hypertensive patients untreated for prolonged periods to determine their usual[1,63] blood pressure. In fact, the current guidelines for the treatment of hypertension[64,65] find their justification in trials done with conventional blood pressure. Our analysis does not indicate to what extent blood pressure should be lowered. The latter issue remains unsettled, because the published studies did not account for systolic pressure or pulse pressure[3] or had blood pressure targets that were too high.[4] Finally, as a meta-regression analysis, our study tests whether and to what extent outcome results of trials depend on blood pressure differences, but does not specifically deal with superiority or inferiority of one drug to another.[66,67]

## CONCLUSION

In the trials in hypertensive patients or in normotensive or hypertensive patients at high cardiovascular risk, blood pressure gradients largely accounted for most—if not all—of the differences in cardiovascular outcome. The hypothesis that in patients with uncomplicated hypertension new drug classes, such as ACE inhibitors, angiotensin II receptor antagonists, or α blockers, might influence cardiovascular outcome over and beyond their blood pressure-lowering effects remains unproved.

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## REFERENCES

1 Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet.* 2000;355:865–872.
2 Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. *Br Med Bull.* 1994;50:272–298.
3 Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet.* 1998;351:1755–1762.
4 UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *Br Med J.* 1998;317:703–713.
5 National Intervention Cooperative Study in Elderly Hypertensives Study Group. Randomized double-blind comparison of a calcium antagonist and a diuretic in elderly hypertensives. *Hypertension.* 1999;34:1129–1133.
6 Brown MJ, Palmer CR, Castaigne A, et al. Morbidity and mortality in patients randomised to double-blind treatment with long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS Study: Intervention as a Goal in Hypertensive Treatment (INSIGHT). *Lancet.* 2000;356:366–372.
7 Hansson L, Hedner T, Lund-Johansen P, et al. Randomised trial of effects of calcium antagonists compared with diuretics and β-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet.* 2000;356:359–365.
8 Hansson L, Lindholm LH, Ekbom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity in the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet.* 1999;354:1751–1756.

9 Agabiti Rosei E, Dal Palù C, Leonetti G, et al. Clinical results of the Verapamil in Hypertension and Atherosclerosis Study. *J Hypertens.* 1997;15:1337–1344.
10 Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension : the Captopril Prevention Project (CAPPP) randomised trial. *Lancet.* 1999;353:611–616.
11 UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *Br Med J.* 2000;317:713–720.
12 The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs. chlorthalidone. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA.* 2000;283:1967–1975.
13 Pitt B, Byington RP, Furberg CD, et al. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation.* 2000;102:1503–1510.
14 The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med.* 2000;342:145–153.
15 MacMahon S, Sharpe N, Gamble G, et al. Randomized, placebo-controlled trial of the angiotensin-converting enzyme inhibitor, ramipril, in patients with coronary or other occlusive arterial disease. *J Am Coll Cardiol.* 2000;36:438–443.
16 Teo KK, Burton JR, Buller CE, et al. Long-term effects of cholesterol lowering and angiotensin-converting enzyme inhibition on coronary atherosclerosis. The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT). *Circulation.* 2000;102:1748–1754.
17 Staessen JA, Wang JG, Thijs L. Cardiovascular prevention and blood pressure reduction: a meta-analysis [published correction appears in *Lancet.* 2002 Jan 26;359:360]. *Lancet.* 2001;358:1305–1315.
18 Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med.* 2001;345:851–860.
19 Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med.* 2001;345:861–869.
20 Parving HH, Lehnert H, Bröchner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med.* 2001;345:870–878.
21 PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood pressure lowering regimen among 6105 individuals with prior stroke or transient ischaemic attack. *Lancet.* 2001;358:1033–1041.
22 Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA.* 1970; 213:1143–1152.
23 Hypertension-Stroke Cooperative Study Group. Effect of antihypertensive treatment on stroke recurrence. *JAMA.* 1974;229:409–418.
24 Smith WM. Treatment of mild hypertension: results of a ten-year intervention trial. *Circ Res.* 1977;40:I98–I105.
25 Management Committee of the Australian Therapeutic Trial in Mild Hypertension. *Lancet.* 1980;1(8181):1261–1267.
26 Amery A, Birkenhäger W, Brixko P, et al. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. *Lancet.* 1985;1(8442):1349–1354.
27 Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *Br Med J.* 1985; 291:97–104.
28 SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA.* 1991;265:3255–3264.
29 Dahlöf B, Lindholm LH, Hansson L, et al. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet.* 1991;338:1281–1285.
30 MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *Br Med J.* 1992;304:405–412.
31 Gong L, Zhang W, Zhu Y, et al. Shanghai trial of nifedipine in the elderly (STONE). *J Hypertens.* 1996;14:1237–1245.
32 Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension [published correction appears in *Lancet.* 1997;350:1636]. *Lancet.* 1997;350: 757–764.
33 Liu L, Wang JG, Gong L, et al. Comparison of active treatment and placebo for older patients with isolated systolic hypertension. *J Hypertens.* 1998;16:1823–1829.
34 Helgeland A. Treatment of mild hypertension: a five year controlled drug trial. *Am J Med.* 1980;69:725–732.
35 Coope J, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. *Br Med J.* 1986;293:1145–1151.
36 Borhani NO, Mercuri M, Borhani PA, et al. Final outcome results of the multicenter isradipine diuretic atherosclerosis study (MIDAS). A randomized controlled trial. *JAMA.* 1996;276:785–791.
37 PATS Collaborative Group. Post-stroke antihypertensive treatment study. A preliminary result. *Chin Med J.* 1995;108:710–717.
38 Sprackling ME, Mitchell JRA, Short AH, et al. Blood pressure reduction in the elderly: a randomised controlled trial of methyldopa. *Br Med J.* 1981;283:1151–1153.
39 Perry HM Jr. Treatment of mild hypertension: preliminary results of a two-year feasibility trial. *Circ Res.* 1977;40(5 suppl 1):I180–I187.
40 Barraclough M, Joys MD, MacGregor GA, et al. Control of moderately raised blood pressure: report of a co-operative randomized controlled trial. *Br Med J.* 1973;3:434–436.
41 Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effect of treatment on morbidity in hypertension: results in patients with diastolic blood pressure averaging 115–129 mm Hg. *JAMA.* 1967;202:116–122.
42 Wolff FW, Lindeman RD. Effects of treatment in hypertension: results of a controlled study. *J Chron Dis.* 1966;19:227–240.
43 Carter AB. Hypotensive therapy in stroke survivors. *Lancet.* 1970;1:485–489.
44 Kuramoto K, Matsushita S, Kuwajima I, et al. Prospective study on the treatment of mild hypertension in the aged. *Jpn Heart J.* 1981;22:75–85.
45 Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the Hypertension Detection and Follow-up Program. I. Reduction in mortality of persons with high blood pressure, including mild hypertension. *JAMA.* 1979;242:2562–2571.
46 Cashin-Hemphill L, Holmvang G, Chan RC, et al. Angiotensin-converting enzyme inhibition as anti-atherosclerotic therapy: no answer yet. *Am J Cardiol.* 1999;83:43–47.
47 Neaton JD, Grimm JRH, Prineas RJ, et al. Treatment of mild hypertension study: final results. *JAMA.* 1993;270:713–724.
48 Casiglia E, Spolaore P, Mazza A, et al. Effect of 2 different therapeutic approaches on total and cardiovascular mortality in a Cardiovascular Study in the Elderly. *Jpn Heart J.* 1994;35:589–600.
49 The IPPPSH Collaborative Group. Cardiovascular risk and risk factors in a randomized trial of treatment based on the beta-blocker oxprenolol: the International Primary Prevention Study in Hypertension (IPPPSH). *J Hypertens.* 1985;3:379–392.
50 Wilhelmsen L, Berglund G, Elmfeldt D, et al. Beta-blockers versus diuretics in hypertensive men: main results from the HAPPHY trial. *J Hypertens.* 1987;5:561–572.

51 Wikstrand J, Westergren G, Berglund G, et al. Antihypertensive treatment with metoprolol or hydrochlorothiazide in patients aged 60 to 75 years. Report from a double-blind international multicenter study. *JAMA.* 1986;255:1304–1310.
52 Estacio RO, Jeffers BW, Hiatt WR, et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med.* 1998;338:645–652.
53 Tatti P, Pahor M, Byington RB, et al. Outcome results of the Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care.* 1998;21:597–603.
54 European Working Party on High Blood Pressure in the Elderly (EWPHE). An international trial of antihypertensive therapy in elderly patients. Objectives, protocol and organization. *Arch Intern Pharmacodyn Ther.* 1985;275:300–334.
55 Davis BR, Cutler JA, Gordon DJ, et al. Rationale and design for the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Am J Hypertens.* 1996;9:342–360.
56 Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet.* 2000;355:253–259.
57 Hedges LV, I Olkin. *Statistical Methods for Meta-Analysis.* San Diego, CA: Academic Press Inc; 1985.
58 Wang JG, Staessen JA, Gong L, et al. Chinese trial on isolated systolic hypertension in the elderly. *Arch Intern Med.* 2000;160:211–220.
59 Staessen JA, Thijs L, Birkenhäger WH, et al. Update on the Systolic Hypertension in Europe (Syst-Eur) Trial. *Hypertension.* 1999;33:1476–1477.
60 Davies MJ. Reactive oxygen species, metallo-proteinases, and plaque stability. *Circulation.* 1998;97:2382–2383.
61 Garg R, Yusuf S, for the Collaborative Group on ACE Inhibitors Trials. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA.* 1995;275:1450–1456.
62 Flather MD, Yusuf S, Køber L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. *Lancet.* 2000;355:1575–1581.
63 MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. Part 1. Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet.* 1990;335:765–774.
64 The Joint National Committee on Prevention Detection Evaluation and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). *Arch Intern Med.* 1997;157:2413–2446.
65 1999 World Health Organization-International Society of Hypertension guidelines for the management of hypertension. Guidelines Subcommittee. *J Hypertens.* 1999;17:151–183.
66 Moser M. Treating hypertension: calcium channel blockers, diuretics, β-blockers, ACE inhibitors: is there a difference? *J Clin Hypertens.* 2000;2:301–305.
67 Moser M, Pickering TG, Weber MA. Roundtable discussion: blood pressure lowering by any means, or do specific medications make a difference? *J Clin Hypertens.* 2001;3:369–375.

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*Kostis (continued from page 65)*

151–183.
11 Moser M, Pickering TG, Weber MA. Roundtable discussion: blood pressure lowering by any means, or do specific medications make a difference? *J Clin Hypertens.* 2001;3(6):369–375.
12 Moser M. Is it time for a new approach to the initial treatment of hypertension? *Arch Intern Med.* 2001;161(9):1140–1144.
13 Hansson L, Lindholm LH, Ekbom T, et al., for the STOP-Hypertension-2 study group. Randomized trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet.* 1999;354:1751–1756.
14 Lindholm LH, Ibsen H, Dahlof B, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet.* 2002; 359(9311):1004–1010.